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Finally, a time and place for electrophysiological testing in critically ill patients?

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ICU-acquired weakness (ICUAW) is a common and debilitating complication of critical illness associated with an increased risk of mortality as well as persistent morbidity in survivors [1–3]. No clear consensus exists regarding the diagnostic criteria for ICUAW. Recent clinical practice guidelines have emphasized the primacy of the physical examination, using a Medical Research Council (MRC) subscore below 48 (maximum score 60 from six bilateral muscle groups) as the current reference standard that has been widely used in studies of ICUAW albeit with important limitations [4]. However, many critically ill patients are not awake and cooperative during their ICU admission, precluding the ability to complete an MRC-based diagnosis of ICUAW [5, 6]. As such, a number of clinicians and investigators have proposed the use of electrophysiological (EP) studies [i.e., electromyography (EMG) and nerve conduction studies (NCS)] to either complement or replace the need for volitional muscle testing in the diagnosis of ICUAW. However, abnormalities in EMG/NCS performed in critically ill patients are extremely common [7–9], and their diagnostic utility and prognostic significance remain uncertain [4] (Table 1).

In an article recently published in *Intensive Care Medicine*, Hermans and colleagues present the results of a prospective study evaluating the diagnostic properties of abnormal compound muscle action potential (CMAP), sensory nerve action potential (SNAP), and spontaneous electrical activity (SEA) derived from EMG/NCS in 730 critically ill patients, 432 of which also were tested for ICUAW using the MRC sumscore [10]. A reduced CMAP on day 8 of ICU admission had high sensitivity (89 %) but low specificity (41 %) for weakness, whereas reduced SNAP and abnormal SEA had low sensitivity (14 and 21 %, respectively) and high specificity (94 and 89 %, respectively). There was no meaningful difference in diagnostic properties of these measurements at day 15. However, only a reduced CMAP at day 8 was significantly associated with increased mortality at 1 year (36 vs. 15 %, $p < 0.001$). This association remained significant after adjustment for ICUAW and other risk factors [odds ratio 2.46; 95 % confidence interval (CI) 1.11–5.45], and a reduced CMAP at day 8 was also significantly associated with a higher 1-year mortality (hazard ratio 2.82; 95 % CI 1.07–7.39). While the results of diagnostic properties of EP studies in critically ill patients are consistent with recent reports [11, 12], this is the first study to demonstrate the independent, long-term prognostic implications of an abnormal CMAP at day 8 of ICU admission.

The mechanism by which reduced CMAP confers increased mortality at 1-year remains unclear. Interestingly, the most logical explanation, that a reduced CMAP identifies patients with ICUAW which itself has been associated with poor outcomes, is not supported by these data as reduced CMAP was associated with 1-year mortality independent of weakness. However, CMAP may be measuring different aspects of the same phenomenon, and CMAP is not solely reflective of muscle injury, but is associated with nerve function as well [13]. Although a reduced CMAP may indeed provide a means to identify

Table 1 Summary of selected studies using electrophysiological testing

Study	Diagnostic	Notes
Bednarik et al. [9], (<i>N</i> = 46) patients	EP signs of neuromuscular involvement in 56 % at 30 days	
Guarneri et al. [7], (<i>N</i> = 92) patients	30 % developed CIP and/or CIM by EP during ICU stay; persistent in 18 patients at ICU discharge	At 1-year follow up: CIM—1 died, 5 recovered completely CIP/CIM—1 died, 1 recovered, 1 remained tetraplegic CIP—1 recovered, 2 persisting ICUAW, 1 remained tetraparetic
Hermans et al. [8], (<i>N</i> = 420) patients	CIP/CIM diagnosis by EP more frequent in CIT group than IIT group (51 vs. 39 %, <i>p</i> = 0.02)	CIP/CIM independent risk factor for prolonged mechanical ventilation (OR 1.85, 95 % CI 1.17–2.93) Independent risk factors for abnormal EP: prolonged infusion of NMBA (OR 2.01, 95 % CI 1.10–3.99), age (OR 0.98 per year, 95 % CI 0.96–0.99), and days of glucocorticoid treatment (OR 0.97 per day, 95 % CI 0.94–0.99)
Weber-Carstens et al. [11], (<i>N</i> = 56) patients	61 % had abnormal dmCMAP indicating a myopathic process within a week after ICU admission Abnormal dmCMAP predicted ICUAW upon awakening with Sn 83 % and Sp 89 %	Abnormal dmCMAP significantly associated with subsequent diagnosis of ICUAW (OR 0.47 per mV, 95 % CI 0.28–0.79)
Wieske et al. [12], (<i>N</i> = 35) patients	Ulnar SNAP <17.6 μ V – Sn 100 % (95 % CI 68–100 %), Sp 79 % (95 % CI 49–95 %) EDB peroneal CMAP <0.43 mV – Sn 80 % (95 % CI 52–96 %), Sp 75 % (95 % CI 48–93 %) Both ulnar SNAP and EDB peroneal CMAP abnormal – Sn 77 % (95 % CI 46–95 %), Sp 100 % (70–100 %)	Diagnostic accuracy for ICUAW may be improved using ICU-based cutoff values (rather than healthy controls)

CI confidence interval, CIM critical illness myopathy, CIP critical illness polyneuropathy, CIT conventional insulin therapy, dmCMAP direct muscle stimulation compound muscle action potential, EDB extensor digitorum brevis, EP electrophysiology, ICU intensive

care unit, ICUAW ICU-acquired weakness, IIT intensive insulin therapy, NMBA neuromuscular blocking agent, OR odds ratio, Sn sensitivity, Sp specificity

high-risk patients with ICUAW, the presence of this abnormality confers additional risk for poor outcomes that may represent a severe form of weakness with different pathophysiology or mediation through other pathways. Whether this represents subclinical weakness or some other form of important neuromuscular dysfunction that is causally associated with mortality requires further investigation. Alternatively, EP study abnormalities such as a reduced CMAP may be an epiphenomenon that is a marker for non-neuromuscular derangements that are causally related to increased mortality.

This study suggests a re-evaluation of the optimal timing and place for EP studies in the diagnosis of ICUAW in critically ill patients. In the recent American Thoracic Society (ATS) guidelines on the diagnosis of ICUAW, the assessment of muscle strength using the MRC sumscore was emphasized as the most commonly used and current primary modality for identifying weak patients [4]. However, given that a reduced CMAP during ICU admission may identify a subgroup of patients at high risk for both morbidity and mortality, its presence may warrant heightened surveillance and follow-up. Given the cost, resources, and relative invasiveness (as compared to physical examination), the ability to screen and diagnose ICUAW earlier with EP testing will only be

useful if it is linked to an important patient-centered outcome for which there is a robust therapeutic intervention that can modify dysfunction if applied early. Currently, there is a paucity of evidence that making a diagnosis of ICUAW, early or not, will lead to improved clinical outcomes. However, this might be a subgroup of patients who warrant early, intensive physical and occupational therapy to prevent further deterioration in neuromuscular function and perhaps lead to improved functional outcomes [14, 15]. Although the provision of early physical and occupational therapy in the ICU appears safe, with few adverse events in previous studies, the concerning results of the AVERT (A Very Early Rehabilitation Trial) study in stroke patients give pause regarding the optimal timing and dose of rehabilitation in acutely ill patients [16]. In addition, there is emerging literature suggesting that pre-existing disability, sarcopenia, and frailty may be important factors related to the patient's inherent ability to recover physical function rather than recovery being primarily dependent on the nature of the underlying injury (Table 1) or application of rehabilitation programs [17, 18]. A clinical trial evaluating the safety and efficacy of early rehabilitation in this high-risk subgroup with a reduced CMAP should be considered. Until then, the use of EP testing in critically ill patients during the first week

of ICU admission could be considered to help clinicians identify patients at higher risk of 1-year mortality, help inform prognostic discussion with patients and their caregivers, and focus attention on patients who may have a more difficult trajectory of recovery following critical illness.

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